

10/568831  
IAP5 Rec'd PCT/PTO 17 FEB 2006

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## PROCESS FOR THE PREPARATION OF METHYLALUMINIUM DICHLORIDE

This invention relates to a method of preparing methylaluminium dichloride and to its use in the preparation of certain fragrant substances.

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Methylaluminium dichloride (MADC) was characterised and procedures for its preparation were published some time ago (for example, *J.Org.Chem.* 5, 106 (1940)). Several later publications described its preparation (for example, *J.Am.Chem.Soc.* 73, 2854 (1951) and US 2,712,546).

10

MADC is potentially useful as a Lewis acid in syntheses, but its use has been hindered by the fact that it is difficult to make consistently and inexpensively on an industrial scale (see, for example, Houben-Weyl "Methoden der organischen Chemie" (Thieme Verlag, 1970), Bd 13/4, pp.59-78).

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It has now been found that it is possible to prepare MADC by a cheap, efficient process that gives a good yield of the compound. It has the additional advantage that the unpurified compound as prepared can be used directly in the preparation of desirable organic compounds. The invention therefore provides a process for the preparation of MADC comprising the steps of

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- (i) reacting by heating a material of the formula  $R_3Al_2X_3$ , where R is C<sub>1</sub>-C<sub>4</sub> alkyl and X is selected from bromine and iodine, with an aluminium-containing material selected from metallic aluminium and a mixture of metallic aluminium and aluminium trichloride in an atmosphere of methyl chloride, with the proviso that, when R is methyl and X is iodine, the aluminium-containing material is a mixture of aluminium and aluminium trichloride; and

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- (ii) when the aluminium-containing material is metallic aluminium, adding aluminium trichloride to this reaction mixture and heating,

to give a crude reaction product; and

- (iii) if desired, obtaining methylaluminium dichloride from this crude reaction product.

The compound of formula  $R_3Al_2X_3$  as hereinabove defined (hereinafter "the sesquihalide") may be any such material, but it is preferably selected from methylaluminium sesquiodide (MASI) and ethylaluminium sesquibromide (EASB). The sesquihalide may be a pure material, but it is preferably the crude mixture of unreacted raw materials and product resulting from the preparation method described by Grosse and Mativy in *J.Org.Chem.* 5, 106 (1940), the details of which are incorporated herein by reference. This describes the MASI preparation, (in this case, the mixture is aluminium, unreacted methyl iodide and MASI), but EASB and the other sesquihalides may be prepared by an exactly analogous method.

This crude sesquihalide mixture is added directly to an aluminium-containing material. The aluminium-containing material is preferably metallic aluminium in particulate form, more preferably it is aluminium gritty. An example of a suitable material is Fluka<sup>TM</sup> 11008 in the Sigma-Aldrich Catalogue. The aluminium-containing material may also be a mixture of metallic aluminium and aluminium trichloride. When the sesquihalide is MASI, the aluminium-containing material must be such a mixture. The weight ratio of Al to  $AlCl_3$  is preferably from 2:1 to 3:1.

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The method comprises the following steps:

- (i) the crude sesquihalide mixture is sprinkled over the aluminium-containing material in an atmosphere of methyl chloride at a pressure of 1 bar, and the mixture heated; and then
- (ii) when the aluminium-containing material is metallic aluminium, the aluminium chloride is added and the mixture is again heated.

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Naturally, when the aluminium-containing compound is an aluminium/aluminium trichloride mixture, step (ii) above is unnecessary.

The following reaction conditions are typical and are given by way of guidance only – the skilled person will know what adjustments will be necessary in each case. Although they are described with reference to the preferred MASI and EASB, the same principles apply for the preparation of all sesquihalides.

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The reaction conditions needed to start the reaction are slightly different, depending on whether MASI or EASB will be used. The starting temperature for MASI may be room temperature (20°-25°C), but slight heating may be needed in the case of EASB (about 45°C). From this point on, the conditions are similar; the temperature is raised to about 115°-120°C and maintained there for 4-6h. At this point, the temperature is lowered to 60°-70°C, and non-polar solvent, typically toluene or cyclohexane, may be added, if need be.

The yield in both cases is typically at least 75% MADC, based on the weight of the aluminium-containing material.

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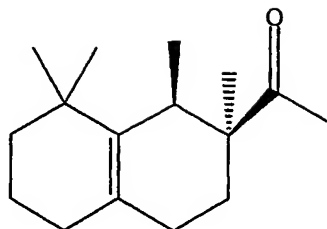
The proportions of crude sesquihalide used are from 0.2-20%, preferably from 0.5-5% by weight of the aluminium-containing material. Without restricting the invention in any way, it is believed that the sesquihalide acts as an activator for the aluminium. It is preferred not to exceed 10% purely for cost reasons – more can be used, but it has no greater effect.

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If desired, pure MADC may be produced from the resulting crude MADC by distillation. However, in another aspect of this invention, this crude MADC may be used in this form to promote a desirable organic reaction. Thus, the invention also provides a method of producing  $\beta$ -Georgywood, comprising the addition of pseudo-Georgywood ( $\psi$ -Georgywood) to the above-mentioned crude MADC.

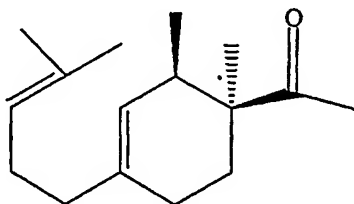
$\beta$ -Georgywood (*cis*-2-acetyl-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethylnaphthalene) is a

fragrance ingredient having the formula I:



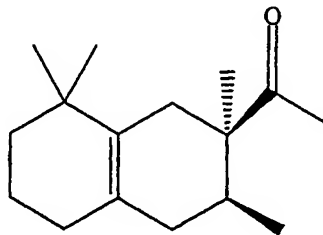
I

This fragrant material is described in United States Patent 5,707,961, the details of which are  
5 incorporated herein by reference. It is known from this patent that Compound I may be prepared by the cyclisation of  $\psi$ -Georgywood (*cis*-1-[1,2-dimethyl-4(4-methyl-pent-3-enyl)-cyclohex-3-enyl]-ethanone – Formula II):



II

The method of preparing the compound of Formula I from that of Formula II is described in  
10 paragraph (d) of Example 1 of the abovementioned US patent. However, that preparation gives a mixture of Compound I and its structural isomer *iso*-Georgywood, shown in Formula III:



III

The compound of Formula I has particularly desirable olfactory properties. It is therefore  
15 desirable to increase the proportion of the compound of Formula I in the mixture. Achieving this using the technology of US 5,707,961 is very difficult.

The process of preparation of  $\beta$ -Georgywood according to the present invention gives a number of distinct advantages:

1. The compound of Formula I is obtained in a yield of more than 80% and in a purity of  
5 higher than 90%. The compound of Formula III is present only in trace amounts (less than 1%).
2. The reaction can be carried out as a "one pot" reaction, that is, all the reactions from the  
initial MADC preparation to the final product reaction can be carried out in a single reaction  
10 vessel, without the need to isolate and purify intermediates.

Both of these are of considerable significance to the preparation of  $\beta$ -Georgywood on a commercial scale.

- 15 A further advantage of the method of this invention is that the compound of Formula I made by the abovementioned process can be easily decoloured, something that is difficult to achieve with products obtained from iodine-containing reagents. For example, a product obtained using MASI as starting material is easily decoloured by stirring or distilling over an acidic clay. In this  
regard, the product obtained by using EASB as starting material is even better, in that  
20 decolorisation is not necessary.

The process is carried out simply by adding Compound II to the crude MADC and heating for about 4 hours at about 60°-70°C.

- 25 The invention is further described with reference to the following non-limiting examples.

Example 1: Preparation of crude MASI, crude MASC and MADC (distilled)

Under nitrogen 18.2g (0.13 mol) methyl iodide and 2g (0.75 mol) aluminium gritty (Fluka™ 110008) are heated to reflux (45°C) for 8-12 h. The resulting crude MASI reaction mixture can be stored under nitrogen for several weeks without loss of activity.

16.2g (0.6 mol) aluminium gritty (Fluka 11008) is placed under 1 atm of methyl chloride (dried over a column filled with KOH) in a sulphonation flask equipped with a reflux condenser and a balloon fixed on the gas-outlet. 0.4ml (ca. 5% w/w) of the above aluminium/methyl iodide/MASI mixture is sprinkled via syringe over the aluminium at 90°C. The reaction starts with a temperature rise to 120°C and formation of liquid MASC. Under stirring, the reaction temperature is maintained at 120°C for 4h (by means of slight cooling and regulation of the methyl chloride flow) until the exothermy and the methyl chloride uptake (56g, 1.1 mol) cease and the theoretical volume of 54ml (d = 1.15) liquid MASC is reached.

The methyl chloride atmosphere is replaced by nitrogen. The black liquid is cooled to 60°C, at which point 29 g (0.22 mol) aluminium chloride is added via a nitrogen-flushed proportioning screw. The black suspension is heated to 120°C and maintained there for 30 min. Formation of MADC can be checked by briefly cooling to under 55°C, at which temperature the reaction mass solidifies. The proportioning screw is replaced by a distillation bridge and the MADC is distilled under 1 atm of nitrogen at bpt. = 157°C to give 69.3g (75% based on aluminium and aluminium trichloride) of colourless MADC, which crystallizes at room temperature in long white needles.

Analytical data:

25 MASI (crude):  $^{27}\text{Al}$ -NMR (neat): 71 ( $W_{1/2}$  = 14800 Hz) ppm.

MASC (crude):  $^{27}\text{Al}$ -NMR (hexane): 177 ( $W_{1/2}$  = 7600 Hz), 136 ( $W_{1/2}$  = 6000 Hz) ppm.

MADC (dist): Fp = 73°C, bp = 157°C.  $^{27}\text{Al}$ -NMR (hexane): 136 ( $W_{1/2}$  = 6000 Hz) ppm.

Example 2: Cyclization of pseudo-Georgywood ( $\psi$ -Georgywood) with commercial MADC:  
(*cis*-2-acetyl-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethylnaphthalene  
( $\beta$ -Georgywood)

5        20g (85 mmol)  $\psi$ -Georgywood dissolved in 100g toluene is added under ice cooling to  
157g (0.21 mol) MADC (1 M in hexane, Aldrich<sup>TM</sup> 29680-5). The mixture is heated to 70°C for  
2-3h, then quenched under ice-cooling with 40g ethanol, then with 2M HCl. The organic phase  
is separated and the aqueous phase extracted with *t*-butyl methyl ether. The combined organic  
layers are washed with conc. NaCl, then with water until pH = 7. The organic phase is dried  
10 over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue is distilled over a  
short Vigreux column (124°C/0.1 Torr) to give 16g (80%) of  $\beta$ -Georgywood as a colorless  
liquid (GC purity ~ 90%).

Analytical data:

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IR (film): 2930 *m*, 1700 *s* (C=O), 1560 *m*, 1377 *m*, 1357 *m*, 1240 *w*, 1220 *w*, 1090 *m*.

GC/MS: 234 (25%, [M]<sup>+</sup>), 219 (15%, [M - CH<sub>3</sub>]<sup>+</sup>), 191 (100%, [M - Ac]<sup>+</sup>, 161 (20%), 135  
(65%), 121 (40%), 105 (40%), 91 (30%), 69 (30%), 43 (55%).

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<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz) : 0.85 (*d*, 3H, *J* = 6.9 Hz, C1-Me), 0.99 (*s*, 3H), 1.02 (*s*, 3H), 1.06  
(*s*, 3H), 1.4-2.2 (10 H, 5 CH<sub>2</sub>), 2.15 (*s*, 3 H, Ac-Me), 2.36 (*q*, 1 H, *J* = 6.9 Hz, C1-H) ppm.

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 400 MHz): 19.1 (CH<sub>2</sub>), 19.7 (CH<sub>3</sub>), 21.0 (CH<sub>3</sub>), 22.5 (CH<sub>2</sub>), 24.9 (CH<sub>3</sub>), 27.7  
25 (CH<sub>2</sub>), 28.9 (CH<sub>3</sub>), 29.4 (CH<sub>3</sub>), 30.8 (CH<sub>2</sub>), 34.0 (C), 35.4 (CH), 40.1 (CH<sub>2</sub>), 50.7 (C), 125.9  
(C=), 136.9 (C=), 214.5 (C=O) ppm.

Example 3: Cyclization of pseudo-Georgywood with crude MADC via MASI activation of aluminium in the presence of  $\text{AlCl}_3$ :  $\beta$ -Georgywood

1.5ml (ca. 0.013 mol) of the aluminium/methyl iodide/MASI mixture prepared according to example 1 is sprinkled via syringe onto a stirred mixture of 42.9g (1.59 mol) of aluminium gritty (Fluka<sup>TM</sup> 11008) and 105.0g (0.79 mol) of aluminium trichloride flakes (Fluka 06220) under 1 atm of methyl chloride at room temperature. The reaction starts almost at once and the initially solid reaction mixture progressively turns into a liquid. The methyl chloride absorption rate is kept approximately constant by gradually increasing the temperature from 25 to 120°C over the next 2h. The reaction is then allowed to proceed at 120°C until no more gas absorption is observed (about 1h). This happens after about 156.0g (3.09 mol) of methyl chloride has been consumed. The crude molten MADC is cooled down to 70°C, the methyl chloride atmosphere is exchanged for an argon one and 810g of dry toluene is added.

The ca. 25 wt% suspension of crude MADC in toluene thus obtained is cooled to 10-15°C and 275.0g (1.06 mol) of 90% pure pseudo-Georgywood is added dropwise. The mixture is heated at 70°C until nearly complete cyclization of pseudo-Georgywood is detected by GC (about 2-3h). The reaction mixture is cooled to 0°C and pumped via a double-tipped needle on to 1.8 kg of ice-cooled 5% aqueous hydrochloric acid. The organic layer is separated, washed until neutral and refluxed for 2h over 30.0g of Montmorillonite K10, an acidic clay. Filtration and concentration of the organic layer under reduced pressure gives crude  $\beta$ -Georgywood, which is rectified over 3 weight% of Montmorillonite K10 through a 2.5 x 20 cm Vigreux column (105-110°C/1 mbar) to give 227g (82.5 % based on pseudo-Georgywood)  $\beta$ -Georgywood (GC-purity 86%) of a yellow colour.

Two further distillations over 10 weight% of paraffin oil and 3 weight% of Montmorillonite K10 give nearly colorless  $\beta$ -Georgywood.

Analytical data: Identical with those from example 2.



Example 4: Cyclization of pseudo-Georgywood with crude MADC  
via EASB activation of aluminium in the presence of  $\text{AlCl}_3$ :  $\beta$ -Georgywood

10.0g (0.37 mol) of aluminium gritty (Fluka<sup>TM</sup> 11008) suspended in 87.7g (0.81 mol) of  
5 ethyl bromide is refluxed for 18 hours at 40°-65°C under nitrogen atmosphere. The crude EASB  
reaction mixture thus obtained can be stored under nitrogen atmosphere for several weeks  
without any loss of activity.

A stirred mixture containing 47.1g (1.75 mol) of aluminium gritty (Fluka 11008) and  
10 115.5 g (0.87 mol) of aluminium trichloride flakes (Fluka 06220) is heated for 30 minutes at 40-  
45°C under 1 atm of methyl chloride. At this temperature, 9ml (ca. 0.05 mol) of the above-  
prepared crude aluminium/ethyl bromide/EASB mixture is sprinkled via syringe on to the  
contents of the vessel and the reaction starts almost at once. The methyl chloride absorption rate  
is kept approximately constant by gradually increasing the temperature from 45 to 120°C over  
15 the next 3h and the initially solid reaction mixture progressively turns into a liquid. The reaction  
mixture is then heated for a further 3h at 120°C, during which period of time gas absorption  
stops after an average amount of 186.0g (3.69 mol) of methyl chloride has been consumed. The  
crude molten MADC is cooled to 70°C, the methyl chloride atmosphere is exchanged for an  
argon one and 810g of dry toluene is added.

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The ca. 27 wt% suspension of crude MADC in toluene thus obtained is cooled to 10-  
15°C and 275.0g (1.06 mol) of 90% pure pseudo-Georgywood is added dropwise. The mixture  
is heated to 70°C until nearly complete cyclization of pseudo-Georgywood is detected by GC  
(about 4 h). The reaction mixture is cooled to 0°C and pumped via a double-tipped needle on to  
25 1.8 kg of ice-cooled 5% aqueous hydrochloric acid. The organic layer is separated, washed until  
neutral and concentrated under reduced pressure to give crude  $\beta$ -Georgywood which is rectified  
through a 2.5 x 31 cm Sulzer DX type column (105-110°C / 1 mbar) to give 224.5 g (82%)  $\beta$ -  
Georgywood (GC purity 89%).

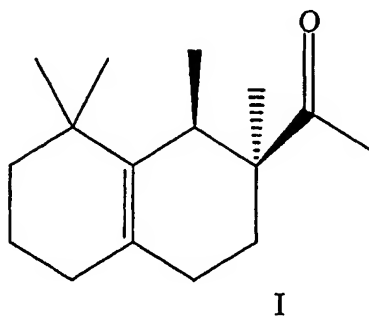
Analytical data: Identical with those from Example 2.

## Claims:

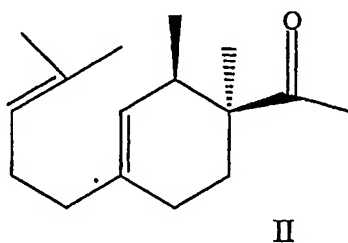
1. A process for the preparation of methylaluminium dichloride by the steps of
  - 5 (i) reacting by heating a material of the formula  $R_3Al_2X_3$ , where R is C<sub>1</sub>-C<sub>4</sub> alkyl and X is selected from bromine and iodine with an aluminium-containing material selected from metallic aluminium and a mixture of metallic aluminium and aluminium trichloride in an atmosphere of methyl chloride, with the proviso that when R is methyl and X is iodine, the aluminium-containing material is a  
10 mixture of aluminium and aluminium trichloride; and
  - (ii) when the aluminium-containing material is metallic aluminium, adding aluminium trichloride to this reaction mixture and heating,  
to give a crude reaction product; and
  - 15 (iii) if desired, obtaining methylaluminium dichloride from this crude reaction product.
2. A method according to claim 1, in which the material of the formula  $R_3Al_2X_3$  is selected  
20 from methylaluminium sesquiodide and ethylaluminium sesquibromide.
3. A method according to claim 1 or claim 2, in which the material of the formula  $R_3Al_2X_3$  is a crude mixture of unreacted raw materials and product resulting from the preparation method described by Grosse and Mativy in *J.Org.Chem.* 5, 106 (1940).  
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4. A method according to any one of claims 1-3, in which the metallic aluminium is particulate metallic aluminium, preferably aluminium gritty.

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5. A method of preparing a compound of the Formula I

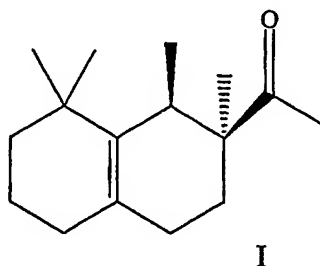


comprising the addition of a compound of Formula II



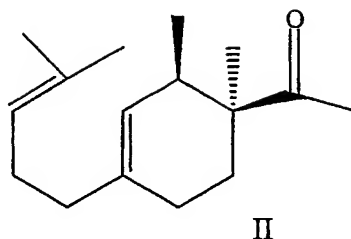
- 5 to the crude reaction product of a reaction according to Claim 1.

6. Use in the preparation of a compound of Formula I



by cyclisation of a compound of Formula II

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of a reaction mixture prepared by the steps of

- 5 (i) reacting by heating a material of the formula  $R_3Al_2X_3$ , where R is  $C_1$ - $C_4$  alkyl and X is selected from bromine and iodine with an aluminium-containing material selected from metallic aluminium and a mixture of metallic aluminium and aluminium trichloride in an atmosphere of methyl chloride, with the proviso that when R is methyl and X is iodine, the aluminium-containing material is a mixture of aluminium and aluminium trichloride; and
- 10 (ii) when the aluminium-containing material is metallic aluminium, adding aluminium trichloride to this reaction mixture and heating.

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 C07F5/06

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

 Minimum documentation searched (classification system followed by classification symbols)  
 IPC 7 C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2 712 546 A (HUBERT HUNTER WILLIAM ET AL) 5 July 1955 (1955-07-05) example 1	1,2,4
X	US 2 848 472 A (COTTLE DELMER L) 19 August 1958 (1958-08-19) example 1	1,2,4
X	US 5 707 961 A (BAJGROWICZ JERZY A ET AL) 13 January 1998 (1998-01-13) cited in the application column 2, lines 48-53; column 3, lines 8-14	5-7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

**\* Special categories of cited documents :**

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*G\* document member of the same patent family

Date of the actual completion of the international search

19 November 2004

Date of mailing of the international search report

09/12/2004

Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/CH2004/000505

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 3  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 3

Claim 3 comprises a reference to a prior art documents with respect to the reactant to be used which does not allow the exact determination of this reactant which makes a search impossible

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 2712546	A	05-07-1955	GB	718198 A	10-11-1954
US 2848472	A	19-08-1958	DE	1041498 B	23-10-1958
			GB	790822 A	19-02-1958
US 5707961	A	13-01-1998	DE	59604205 D1	24-02-2000
			EP	0743297 A1	20-11-1996
			ES	2142512 T3	16-04-2000
			JP	8319250 A	03-12-1996